Safety and Efficacy of BIBF 1120 in Patients with Idiopathic Pulmonary Fibrosis

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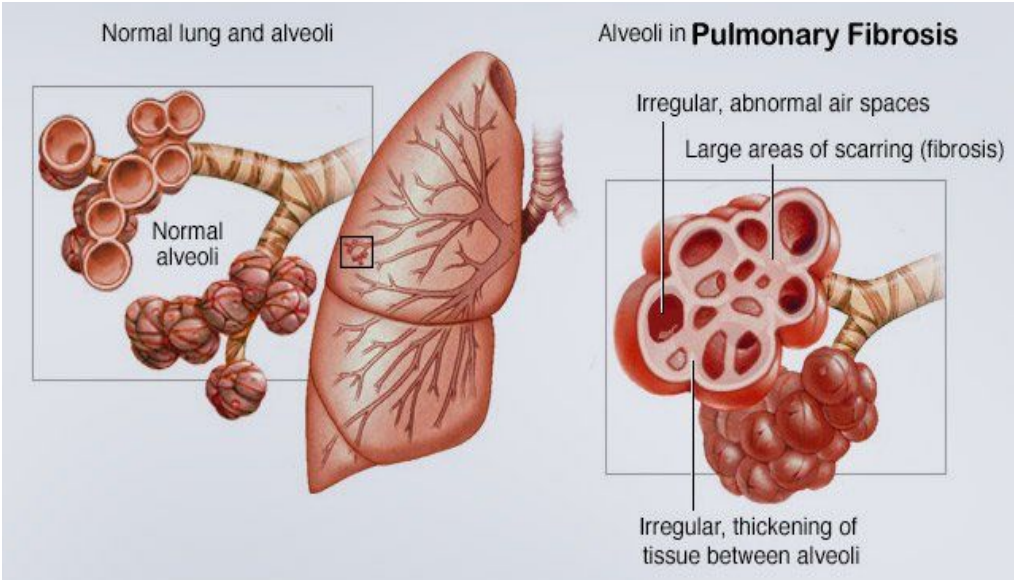
What is Pulmonary Fibrosis?

- An idiopathic chronic lung disease
- Results in irreversible fibrotic scarring of lungs
- The tissue around and between the air sacs and alveoli thickens and scars.
- Lack of oxygen circulation
- Manifests between ages 50-70



Seriousness and Staging of Pulmonary Fibrosis

- There are no formal stages; conditions worsen over time.
- Described as mild, moderate, severe, or very severe.
- Physicians use different identifying factors:

-Pulmonary function tests (PFTs) -High resolution CT scans.

-Six-minute walk test

Gap model scoring system uses gender, age, and physiology to stage Pulmonary Fibrosis.

Prevalence of Pulmonary Fibrosis

- 13-20/100,000 people worldwide
- Very rarely passed down genetically
- 100,000 people affected in the United States

Incidence of Pulmonary Fibrosis

- 30,000-40,000 new cases per year

Current Treatment for Pulmonary Fibrosis

- Pirfenidone and Nintedanib (BIBF 1120)
  - **Nintedanib side effects:** diarrhea and nausea
  - **Pirfenidone side effects:** nausea, loss of appetite, and skin rash from the sun

    ➔ Blood tests conducted to determine liver functioning with both medications
- Oxygen therapy
- Lung transplant
  - Potential complications: organ rejection and an increased risk of infections

Cost of Intervention Treatment vs. Other Pulmonary Fibrosis Treatments

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Nintedanib: The annual cost of this medication can reach up to $96,000, according to GoodRx. No GoodRx coupons available.

Pirfenidone: For an uninsured patient, it will cost $509.16

- **Oxygen therapy** is an extra expense with the price depending on the patient's insurance.
- **Lung transplants** may be a necessary option, but the most costly.

Risk factors for Pulmonary Fibrosis

Long-term exposure to:

- Toxin/pollutants
  - Silica dust, hard metal dust, mold
- Radiation therapy
- Medical treatments
  - Chemotherapy, medications for heart disease, certain antibiotics

Medical conditions:

- Lupus, pneumonia, rheumatoid arthritis

Nintedanib Dosage and Administration

- BIBF 1120 (Nintedanib) is an enzyme blocker needed for cell growth, and may prevent the growth of new blood vessels that tumors need to grow
- Dose: 150 mg, administered orally, twice daily, in patients with Idiopathic Pulmonary Fibrosis (IPF)

Primary Outcome Measure

- Rate of decline of Forced Vital Capacity over 52 weeks
  - FVC is the total amount of air exhaled during spirometry.
    - Lower the percentage, Higher severity

Test comparison of FEV1/FVC ratio outcomes allow healthcare providers to determine whether your condition is:

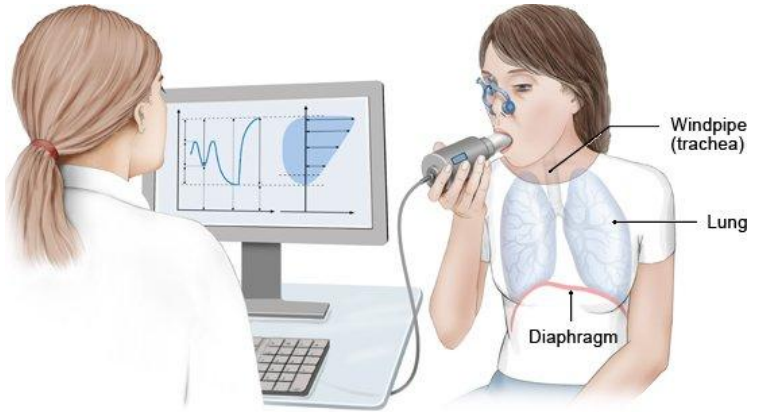
Normal: Airflow and lung volume are within the expected range.

Restrictive: Airflow is normal but lung volume is decreased.

Obstructive: Airflow is decreased but lung volume is normal.

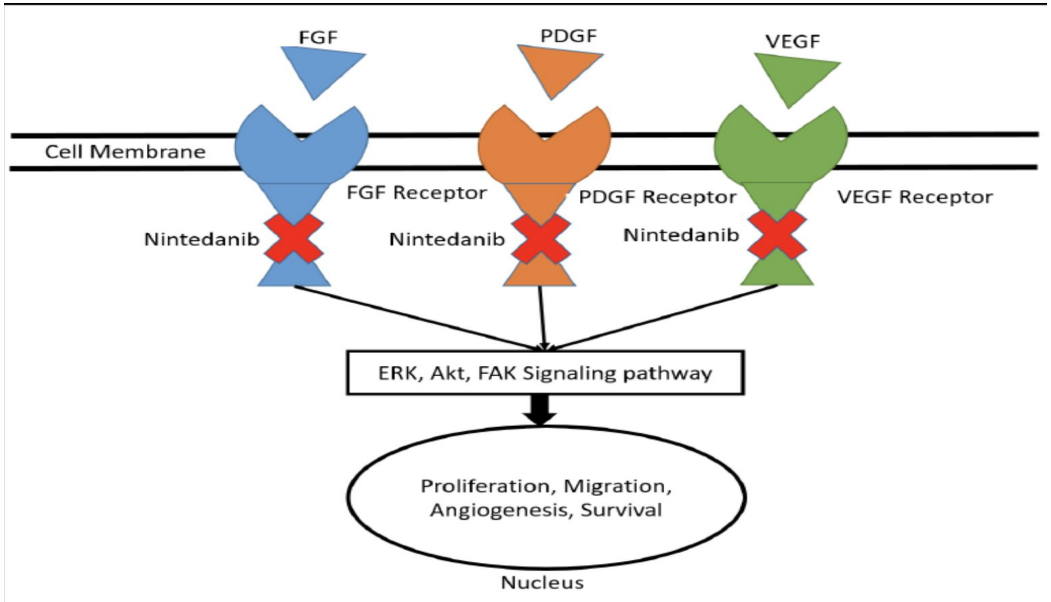
Mixed: Airflow and lung volume are both decreased.

Test	Predictive (normal) values	Abnormal values
FEV1 or FVC	Equal to or greater than 80%	Mild: 70-79% Moderate: 60-69% Severe: Under 60%
FEV1/FVC ratio	Equal to or greater than 70%	Mild: 60-69% Moderate: 50-59% Severe: Under 50%



Mechanism of Action

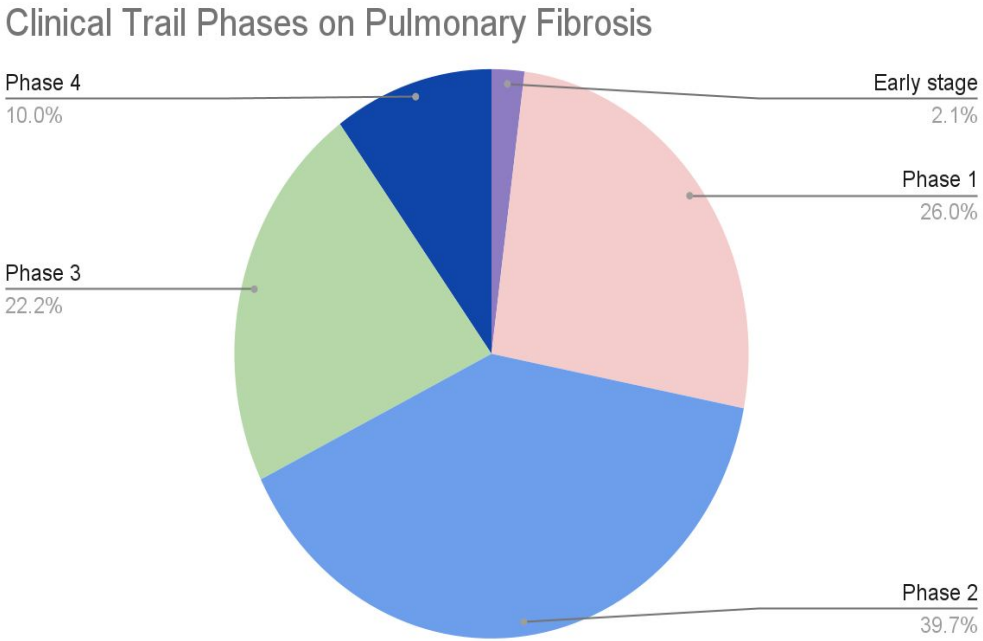
1. BIBF 1120 binds to and blocks the activity of VEGFR, PDGFR, FGFR which are key signaling pathways involved in cell proliferation, migration, and angiogenesis (new blood vessel formation)
2. By inhibiting these kinases, BIBF 1120 reduces the production of extracellular matrix proteins like collagen, which is critical in the development of fibrosis.



Study Goal and Objective

- **Goal:** to determine the efficacy and safety of nintedanib (BIBF 1120) to treat patients with idiopathic pulmonary fibrosis
  - Ideal outcome would be if positive effects on lung function were observed with the use of the drug compared to the placebo
- **Objective:**
  - Nintedanib (BIBF 1120) was assessed in patients over the age of 40 diagnosed with IPF
  - A total of 551 subjects were recruited with 220 receiving the placebo and 331 receiving the BIBF 1120
  - Double-blind study
- Effects were measured using the annual rate of decline in FVC to determine whether the nintedanib 150 mg BID was more effective than the placebo

Database Analysis

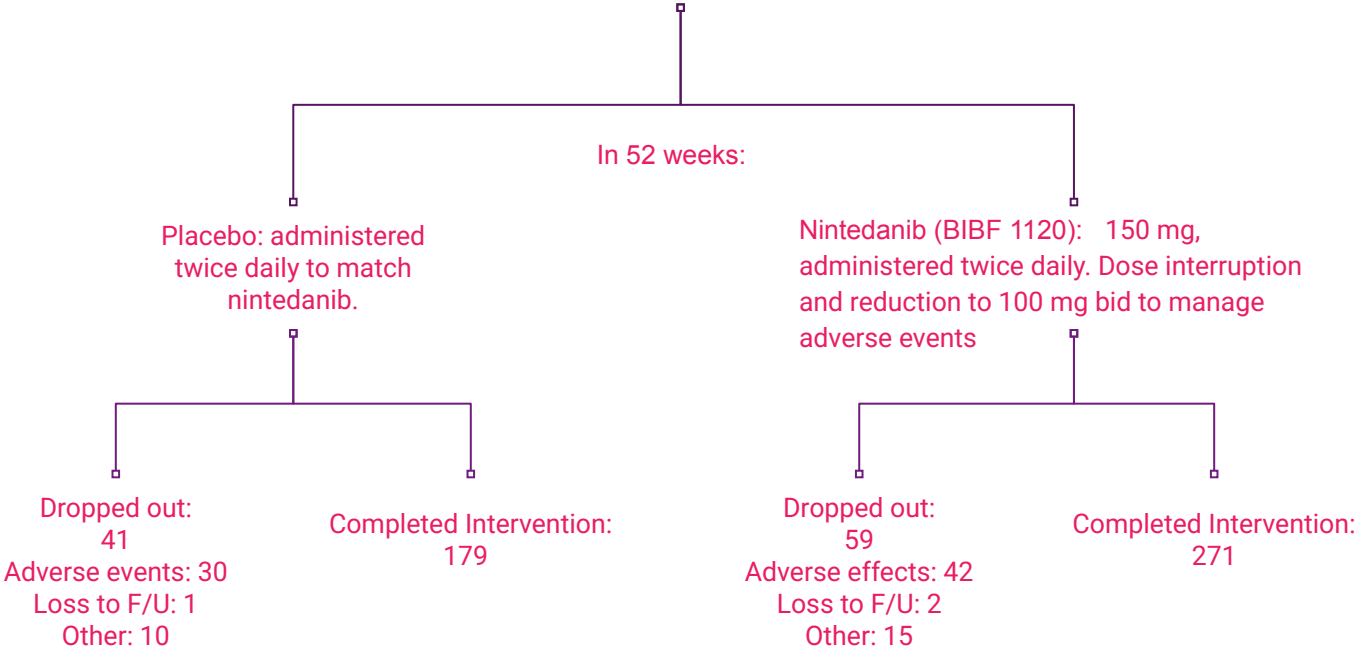


- 2,379 Total studies on pulmonary fibrosis
- 1,618 Interventional studies
- 748 Observational studies

- Only 10% of interventions make it to phase 4, while 39.7% remained in Phase 2, which is where 70% of studies fail.

- Effective and affordable treatment options to cure individuals with pulmonary fibrosis is likely limited.

Safety and Efficacy of BIBF 1120 at High Dose in Idiopathic Pulmonary Fibrosis Patients



Out of 550 participants, 100 Participants dropped out total.

Inclusion Criteria:

- Age ≥ 40
- Diagnosed with IPF within 5 years
- Combination of High Resolution Computerized Tomography (HRCT) pattern consistent with IPF diagnosis
- DLco (adjusted for Hb) of 30 to 79% predicted of normal
  - DLco = diffusion capacity of carbon monoxide
- FVC ≥ 50% of normal

Exclusion Criteria:

- Abnormal aspartate Aminotransferase (AST) or alanine aminotransferase (ALT)
- Abnormal bilirubin levels
- Relevant airway obstruction
- Patients needing a lung transplant
- Patients who have recently experienced heart issues such as myocardial infarction, unstable angina, or thrombotic events.
- Patients with high bleeding risk
- Abnormal prolongation of prothrombin time or partial thromboplastin time
- Patients who recently received, N-Acetyl Cysteine, prednisone, pirfenidone, azathioprine, cyclophosphamide, cyclosporine A

Results

Placebo group:

- Patients analyzed: 219
- Lost of lung function (mean): -207.32 mL/year

Nintedanib group:

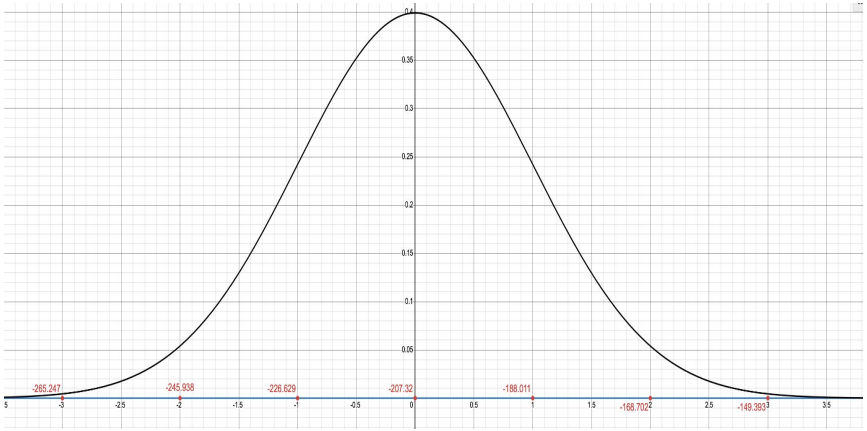
- Patients analyzed: 329
- Lost of lung function (mean): -113.59 mL/year
  ➔ The negative values indicate a progressive lung function loss over time

Mean difference: 93.73 mL/year

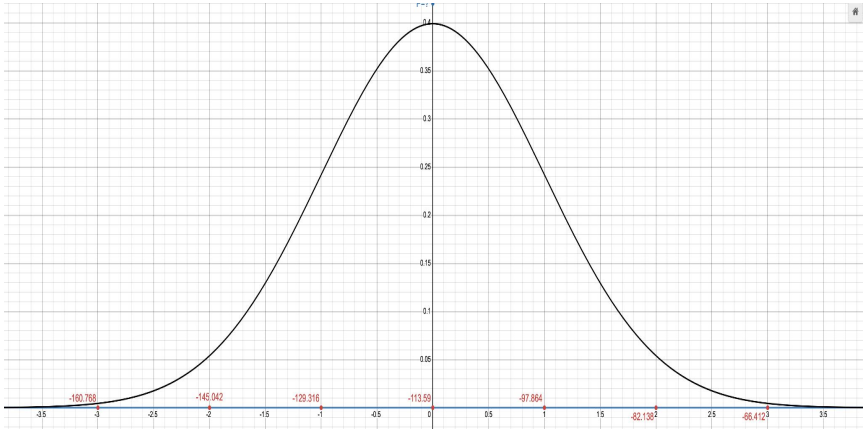
P-value: 0.0002

Normally Distributed Bell Curves for Intervention vs. Placebo

FVC annual decline given placebo



FVC annual decline given Nintedanib



Adverse Effects

Serious:

Placebo = 72/219 (32.88%)

- Anemia (0.91%), angina pectoris (0.91%), respiratory failure (2.28%), pulmonary hypertension (1.37%), respiratory tract infection (1.37%), syncope (0.91%), dyspnea (1.37%), etc.

Nintedanib = 98/329 (29.79%)

- Acute myocardial infarction (0.61%), cardiac failure (0.61%), myocardial infarction (0.91%), hemorrhoids (0.61%), sudden death (0.30%), pneumonia (5.47%), pulmonary hypertension (1.82%), etc.

Non-Serious:

Placebo = 193/219 (88.13%)

- Nasopharyngitis (15.53%), fatigue (9.13%), arthralgia (5.02%), hypertension (5.02%), etc.

Nintedanib = 308/329 (93.62%)

- Abdominal pain (9.12%), diarrhea (62.92%), nausea (26.14%), weight gain (11.25%), decreased appetite (12.77%), headache (6.69%), etc.

Interpretation

- Our findings are statistically significant. The results are based on **Forced Vital Capacity** (FVC) values over time (mL/year), which represents the maximum amount of air a person can forcefully exhale after a deep breath.
- **Placebo group**: loss of 207.32 mL of lung capacity/year
- **Nintedanib 150 mg group:** lost 113.59 mL of lung capacity/year
- Significant reduction in the rate of lung function decline by **93.73 mL** per year in favor of nintedanib.
- However, 93.6% of participants experienced non-serious adverse effects from the medication, and 29.8% experienced serious adverse effects.

  -> This highlights the severity of the disease, as it is a chronic condition that worsens over time, while also indicating that the medication used has associated side effects.

Supplemental Article #1:

Effects of nintedanib on symptoms in patients with progressive pulmonary fibrosis

- 52 week randomized control trial using the same intervention and dosage as our main clinical trial.
- Unit of measurement: The Living with Pulmonary Fibrosis (L-PF) questionnaire
- Adverse events were not reported
- Out of 663 participants, 332 Received the 150 mg nintedanib BID and 331 received the placebo. Patients who discontinued intervention were moved to placebo group and still completed follow up visits. Instead of completing the questionnaire, their FVC over the 52 weeks was measured.
- According to the questionnaire statistics, the intervention shows decreased dyspnoea, fatigue and cough over 52 weeks compared to the placebo group. This shows that nintedanib is effective in decreasing the worsening of pulmonary fibrosis.

Supplemental Article #2:

"Efficacy and Safety of Nintedanib Co-administered With Sildenafil in Idiopathic Pulmonary Fibrosis Patients With Advanced Lung Function Impairment"

- A 24-week, double-blind, randomized controlled trial evaluating the efficacy of oral Nintedanib 150 mg in combination with oral Sildenafil 20 mg compared to Nintedanib 150 mg alone in patients with idiopathic pulmonary fibrosis (IPF).
- Unit of measure: A 24-item test known as the UCSD SOBQ gauges breathlessness on a scale of 0 to 5,
    - 0 = no breathlessness at all and 5 = extreme breathlessness / being too breathless to complete the task.

➔ 274 participants, only 212 complete the trial

- Adverse events:
    - **Nintedanib + Placebo group:** Pneumonia, cardiac and gastrointestinal disorders reported in 8.82% of the 136 participants. These events resulted in 28 drop-outs.
    - **Nintedanib + Sildenafil group**: Hepatobiliary disorders, dyspnea, and blood and lymphatic system disorders reported in 8.76% of the 137 participants. It resulted in 20 drop-outs..

- The **Nintedanib + Placebo group** obtained a mean of 4.40 and the **Nintedanib + Sildenafil group** obtained a mean of 1.42.
- Results indicate that the addition of Sildenafil was associated with a lower occurrence or severity of the measured outcome compared to Nintedanib alone.

Recommendations on Improvements

- Time frame: 52 weeks is too long. This lead to higher drop-out rates among participants receiving the placebo medication. Pulmonary fibrosis can be lethal if left untreated, and only receiving a placebo for 52 weeks could be life threatening. For this reason, the study should have been shorter to account for safety concerns.
- The longevity of the study also affected the compliance among participants receiving the intervention resulting in further drop-out rates in those who did not immediately see an increase in their FVC.

Dosages, branches, intervention, design, and unit of measure were appropriate. Age range of an older population was appropriate since age is a risk factor for pulmonary fibrosis.

Next Steps

- BIBF 1120 would be recommended as an intervention as it led to positive effects on lung function
  - The FVC annual rate of decline was less in those who were taking the medication as opposed to those taking the placebo
  - A greater proportion of the placebo group faced serious adverse effects and dropped the study due to these adverse effects compared to the intervention group

Citations:

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